REMARKS

The status of the application is as follows: claims 1-9 and 25-38 are pending and were rejected in the Office Action mailed June 28, 2007; claims 10-24 were withdrawn from consideration pursuant to an earlier election; and claims 1-9 and 25-38 are amended by this Response.

Applicant acknowledges with appreciation the Examiner's withdrawal of the prior rejections. The Examiner has, however, rejected the pending claims on new grounds. Applicant respectfully traverses the new grounds of rejection.

Claim Objections

The Examiner objected to claims 8 and 9 as being of improper dependent form for failing to further limit the subject matter of claim 1 with regard to the biomolecule.

Claim 1 recites "the maleic anhydride compound having an exposed carbonyl for reversible covalent binding to a biomolecule." The Examiner is correct in that the biomolecule itself is not positively recited as an element of claim 1. The reference to biomolecule limits the nature of the exposed carbonyl, *i.e.*, it must be capable of covalent binding to a biomolecule. Claims 8 and 9 have been amended to recite that the biomolecule to which maleic anhydride compound is bound comprises either a biomolecule having an amine, or a protein, respectively.

Withdrawal of the objection to claims 8 and 9, as amended, is respectfully requested.

Claim Rejections

1. 35 U.S.C. §102(e)

In the Office Action, the Examiner rejected claims 1-3, 5-9, 25 and 27-38 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,590,071 to Shen & Heiati (the '071 Patent). The Examiner cited specifically the reference to "liposomes" at col. 10, line 20 as evidence of the teaching of a substrate and col. 6, Formula II and Formula III as evidence of the teaching of a maleic anhydride compound. With regard to claim 7, the Examiner referenced the

term "binders" at col. 13, line 28 as evidence of a solid support. Applicant respectfully disagrees with the Examiner's interpretation of the teachings of the '071 Patent and the relevance thereof to the claims of the Subject Application.

For a reference to anticipate a claim under 35 U.S.C. §102, it must disclose, either expressly or inherently, each and every element of the claim. MPEP §2131. The '071 patent does not disclose, expressly or inherently, every element of claims 1-3, 5-9, 25 and 27-38.

The '071 patent describes a drug-carrier conjugate useful for the uptake and *in vivo* release of biologically-active amino group containing compounds. Formula II, shown in col. 6, lines 1-23, shows a maleic anhydride core with an R^2 group, which may be an alkyl, and a second component shown as a carbon attached to either a S or O molecule which is attached either directly or through a carbon/oxygen and optionally a bridging amino acid, to a lipophilic group, designated as R^3. Biologically active amino group containing substances, such as amine-containing drugs, amino acids, peptides and proteins are reacted with the Formula II compound *in vitro* to form an amide bond to form the Formula I compound. That conjugate is administered to a mammal (*see* col. 12, lines 36-39) as part of a pharmaceutical composition (*see* col. 12, lines 48-50) by a variety of means, including parenteral administration (*see* col. 13, line 3).

The Examiner referred to col. 10, line 20 as evidence of a support. The term "liposomes" is one of several terms within a parenthetical identifying the form in which the Formula I conjugate may be administered to a mammal to increasing the absorption or to prolong blood and tissue retention in the mammal of the biologically active substance. The '071 patent is silent as to any mechanism for the various forms of administration. Specifically, there is no teaching that the functional group of the maleic anhydride at one of the 2 or 3 position is covalently bound to a surface of the substrate. Liposomes are lipid bilayers and it is well known in the art that they are non covalent structures and do not form covalent bonds. *See* L. Stryer, BIOCHEMISTRY, pp. 284 and 290, Third Edition, W.H. Freeman and Company publishers, (1988), copy enclosed. Therefore, the teaching in the '071 patent to use a liposome to assist in the *in vivo* delivery of a drug does not disclose the concept of covalently binding a maleic anhydride through a functional group at the 2 or 3 position of the maleic anhydride for use in a device for the *in vitro* separation of biomolecules from a solution.

The Examiner referred to col. 13, line 21 for disclosure of a solid support to which the substrate may be attached. That paragraph contains a description of the manner in which pharmaceutical preparations are manufactured; by mixing, granulating, dragee-making, dissolving or lyophilizing processes wherein the active compounds of the pharmaceutical preparation, which would be the biologically active amino group containing substances, are combined with solid excipients, examples of which are listed in the following paragraph beginning at line 25. The solid excipient particles are mixed with the biological active compounds. None of the listed manufacturing processes would bind the excipient to the biologically active compound. They are simply mixed together.

After the conjugate is processed as described, the pharmaceutical preparation is administered to a person or other mammal. The desired effect, as described in col. 7, lines 59-67, is that the lipophilic group, R_3 will bind *in vivo* to the apical side of a cell membrane to facilitate the transport of the conjugate through the cell membrane. Once inside the cell membrane, the biologically active amine containing compound is released into the fluid of the cell by hydrolysis of the amide bond. After the release, the conjugate forms Formula III. It does not revert to Formula II for re-use. *See* Figs. 9-11. Note from the schematics in the Figures that the hydrolysis occurs *in vivo* at a pH of about 7.4.

Applicant's invention is directed to a device for the *in vitro* separation of biomolecules from other components in a solution. The claims have been amended to clarify the distinction. No new matter is introduced by the amendments. The fact that the biomolecule capture device is a device for the *in vitro* separation of biomolecules from a solution is apparent throughout the Specification. See for example, page 2, lines 26-30, page 5 relating to the suitable substrates and page 6 relating to solid supports and the shape of the substrate or support, page 10, lines 1-2 and page 13, lines 15-20. It is not a vehicle for administration of a drug to a mammal. Applicant's device includes a solid substrate to which one end of a maleic anhydride is covalently bound. The other end of the maleic anhydride reversibly attaches to a desired biomolecule when a solution containing such biomolecules and other compositions are brought into contact with the bound maleic anhydride of the capture device.

As stated above, the '071 patent does not disclose, expressly or inherently, every element of claims 1-3, 5-9, 25 and 27-38. Withdrawal of the rejection of claims 1-3, 5-9, 25 and 27-38 under §102(e) is requested.

2. 35 U.S.C. §103(a)

The Examiner rejected claims 1-9 and 25-38 under 35 U.S.C. §103(a) as being unpatentable over Boucher, U.S. Patent No. 6,264,975 (the "'975 patent") in view of the '071 patent.

The '975 patent describes a method of hydrating mucosal membranes and more specifically, the topical application of a sodium channel blocker to the nasal mucosal membrane in an amount effective for inhibiting reabsorption of water. The Examiner cites the reference to "mucosal surface" in the title of the '975 patent as evidence of the teaching of a substrate having a surface. The Examiner acknowledges that the '975 patent does not disclose maleic anhydride compounds covalently attached to the nasal mucosal surface, but asserts that a person of ordinary skill in the art would find it obvious "to complement Boucher's device with Shen & Heiati's maleic anhydride compound because Shen & Heiati discovered compounds capable of sequentially penetrating biological membrane, and thereafter, releasing drugs." The Examiner characterized the '071 patent as providing a description of maleic anhydride compounds covalently attached to liposome surfaces and cited col. 6, Formula II, X, R^3 and col. 10, line 20.

The test for patentability under 35 U.S.C. §103(a) requires that (1) the scope and content of the prior art be determined; (2) differences between the prior art and the claims at issue be ascertained; and (3) the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *See* "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.," 72 Fed. Reg. 57526, 57527 (Oct. 10, 2007) (hereinafter "Guidelines"). In an obviousness analysis, the controlling question is simply whether the differences between the prior art and the claimed invention are such that, despite the differences, the invention would have been obvious to one of ordinary skill in the art. *See* Guidelines at 57528 (The proper analysis is whether the claimed invention would have been

obvious to one of ordinary skill in the art after consideration of all the facts, particularly the differences between the claims and the prior art).

Ascertaining the differences between the prior art and the claims requires consideration of both the claimed invention and the prior art as a whole. MPEP §2141.02. Further, a proposed combination of prior art can not change the principal of operation of the prior art and can not render the prior art unsatisfactory for its intended purpose. MPEP §2143.01, Parts V and VI.

In Formula II, X is oxygen or sulfur and R^3 is a lipophilic group. Lipophilic group is defined, in the '071 patent to mean "a naturally occurring lipid per se, a hydrophobic branched or unbranched hydrocarbon comprising about 4 to about 26 carbon atoms, ... a fatty acid or ester thereof, or a surfactant." Membranes consist mainly of lipids and proteins that form lipid bilayers. Importantly, membranes are noncovalent assemblies. *See* L. Stryer, BIOCHEMISTRY, pp. 284 and 290, Third Edition, W.H. Freeman and Company publishers, (1988). Assuming, *arguendo*, that Formula II of the '071 patent was applied to the mucosal membrane of someone's nasal passages, the combination would not produce a device for the *in vitro* separation of biomolecules from a mixture comprising a substrate having a surface and a maleic anhydride compound covalently bound through a functional group at one of a molecular 2 or 3 position of the maleic anhydride to the surface of the substrate. In the combination the Examiner proposes, the Formula II compound would not be covalently bound to the nasal passages. If it were, the Formula I - biologically active amine containing compound conjugate of the '071 patent could not be absorbed into the cell, thereby destroying the intended function of the '071 patent. The same outcome would be true for the '975 patent. If the Formula I, II or III of the '071 patent were to be topically applied to someone's nasal passages, the mucosal membrane would not be hydrated, thereby destroying the intended function of the '975 patent. One skilled in the art would not be motivated to make the proposed combination.

However, even if the combination were to be made, the combination would not lead to applicant's device. Applicant's device is not directed to penetrating biological membranes, sequentially or otherwise, to release biologically active amine containing compounds in the interior of a cell. Applicant's device is not directed to hydrating mucosal membranes. Neither

reference is directed to the *in vitro* separation of biomolecules from a solution. Neither reference teaches that the functional group of a maleic anhydride is covalently bound to a substrate.

When considering the fact that the '975 patent doesn't relate at all to maleic anhydrides, that neither patent discloses a device for the *in vitro* separation of biomolecules from a solution, and neither discloses covalently binding a maleic anhydride to the surface of a substrate through a functional group at the 2 or 3 position of the maleic anhydride, it is clear that the differences between the claims of the Subject Application and the prior art are not insignificant and are of a character that would not have been obvious to a person skilled in the art at the time of the invention. The features recited in the claims of the Subject Application are not disclosed or otherwise suggested by the references of record or the knowledge generally available to one of ordinary skill in the art. Applicant submits that these inventive features render the claimed invention as a whole non-obvious over the art of record.

Withdrawal of the rejection of claims 1-9 and 25-38 under 35 U.S.C. §103(a) is requested.

Conclusion

Reconsideration and allowance of all pending claims in light of the foregoing is earnestly solicited. If the undersigned can be of assistance in advancing the Subject Application to allowance or in addressing any issue the Examiner believes remains, the Examiner is urged to contact the undersigned at the number set forth below.

Respectfully submitted,

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BIOCHEMISTRY

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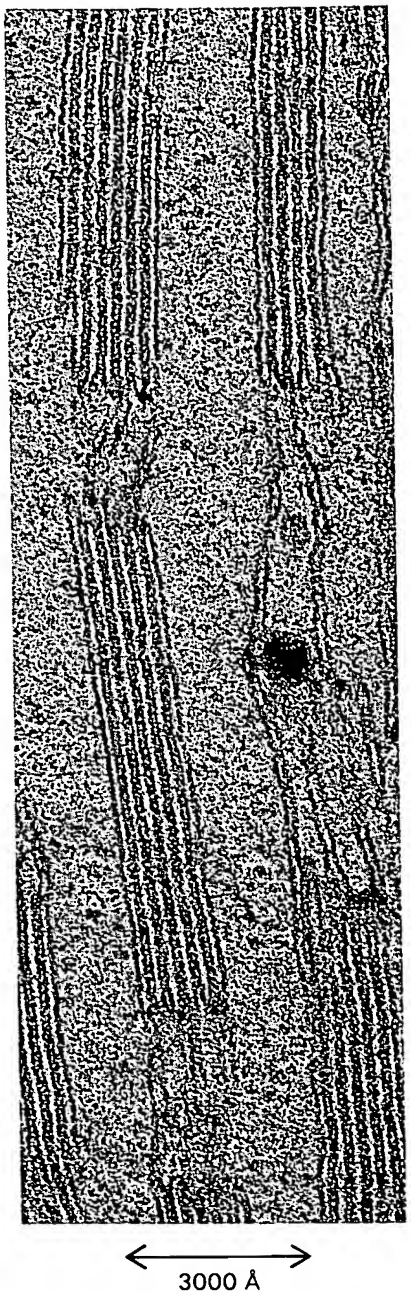

Figure 12-2
Light is converted into chemical-bond energy by photosynthetic assemblies in the thylakoid membranes of chloroplasts. [Courtesy of Dr. M. C. Ledbetter.]

plasts (Figure 12-2), whereas *oxidative phosphorylation,* in which adenosine triphosphate (ATP) is formed by the oxidation of fuel molecules, takes place in the inner membranes of mitochondria. These and other membrane processes will be discussed in detail in later chapters. This chapter deals with some essential features that are common to most biological membranes.

COMMON FEATURES OF BIOLOGICAL MEMBRANES

Membranes are as diverse in structure as they are in function. However, they do have in common a number of important attributes:

1. Membranes are *sheetlike structures,* only a few molecules thick, that form *closed boundaries* between compartments of different composition. The thickness of most membranes is between 60 and 100 Å.

2. Membranes consist mainly of *lipids* and *proteins*. The weight ratio of protein to lipid in most biological membranes ranges from 1:4 to 4:1. Membranes also contain *carbohydrates* that are linked to lipids and proteins.

3. *Membrane lipids are relatively small molecules* that have both a hydrophilic and a hydrophobic moiety. These lipids spontaneously form *closed bimolecular sheets* in aqueous media. These *lipid bilayers* are barriers to the flow of polar molecules.

4. *Specific proteins mediate distinctive functions of membranes.* Proteins serve as pumps, gates, receptors, energy transducers, and enzymes. Membrane proteins are embedded in lipid bilayers, which create suitable environments for their action.

5. Membranes are *noncovalent assemblies*. The constituent protein and lipid molecules are held together by many noncovalent interactions, which are cooperative.

6. Membranes are *asymmetric*. The two faces of a membrane are different.

7. Membranes are *fluid structures*. Lipid molecules diffuse rapidly in the plane of the membrane, as do proteins, unless they are anchored by specific interactions. In contrast, they do not rotate across the membrane. Membranes can be regarded as *two-dimensional solutions of oriented proteins and lipids.*

PHOSPHOLIPIDS ARE THE MAJOR CLASS OF MEMBRANE LIPIDS

Lipids differ markedly from the other groups of biomolecules considered thus far. By definition, lipids are water-insoluble biomolecules that are highly soluble in organic solvents such as chloroform. Lipids have a variety of biological roles: they serve as fuel molecules, highly concentrated energy stores, signal molecules, and components of membranes. The first three roles of lipids will be discussed in Chapters 20 and 23. Here, the concern is with lipids as membrane constituents. The three major kinds of membrane lipids are *phospholipids, glycolipids,* and *cholesterol.*

character. The formation of lipid bilayers from glycolipids and phospholipids is a rapid and spontaneous process in water. *Hydrophobic interactions are the major driving force for the formation of lipid bilayers.* Recall that hydrophobic interactions also play a dominant role in the folding of proteins in aqueous solution. Water molecules are released from the hydrocarbon tails of membrane lipids as these tails become sequestered in the nonpolar interior of the bilayer. Furthermore, there are *van der Waals attractive forces* between the hydrocarbon tails. These forces favor close packing of the tails. Finally, there are *electrostatic and hydrogen-bonding attractions between the polar head groups and water molecules.* Thus, lipid bilayers are stabilized by the full array of forces that mediate molecular interactions in biological systems.

LIPID BILAYERS ARE NONCOVALENT, COOPERATIVE STRUCTURES

Another important feature of lipid bilayers is that they are *cooperative structures.* They are held together by many *reinforcing, noncovalent interactions.* Phospholipids and glycolipids cluster together in water to minimize the number of exposed hydrocarbon chains. A pertinent analogy is the huddling together of sheep in the cold to minimize the area of exposed body surface. Clustering is also favored by the van der Waals attractive forces between adjacent hydrocarbon chains. These energetic factors have three significant biological consequences: (1) lipid bilayers have an inherent tendency to be *extensive*; (2) lipid bilayers will tend to *close on themselves* so that there are no edges with exposed hydrocarbon chains, which results in the formation of a compartment; and (3) lipid bilayers are *self-sealing* because a hole in a bilayer is energetically unfavorable.

LIPID BILAYERS ARE HIGHLY IMPERMEABLE TO IONS AND MOST POLAR MOLECULES

The permeability of lipid bilayers has been measured in two well-defined synthetic systems: lipid vesicles and planar bilayer membranes. These model systems have been sources of insight into a major function of biological membranes—namely, their role as permeability barriers. The key finding is that lipid bilayers are inherently impermeable to ions and most polar molecules.

Lipid vesicles (also known as *liposomes*) are aqueous compartments enclosed by a lipid bilayer (Figure 12-12). They can be formed by suspending a suitable lipid, such as phosphatidyl choline, in an aqueous medium. This mixture is then *sonicated* (i.e., agitated by high-frequency sound waves) to give a dispersion of closed vesicles that are quite uniform in size. Alternatively, vesicles can be prepared by rapidly mixing a solution of lipid in ethanol with water. This can be accomplished by injecting the lipid through a fine needle into an aqueous solution. Vesicles formed by these methods are nearly spherical in shape and have a diameter of about 500 Å. Larger vesicles (of the order of 10^4 Å, or 1 μm, in diameter) can be prepared by slowly evaporating the organic solvent from a suspension of phospholipid in a mixed solvent system.

Ions or molecules can be trapped in the aqueous compartment of lipid vesicles by forming the vesicles in the presence of these substances

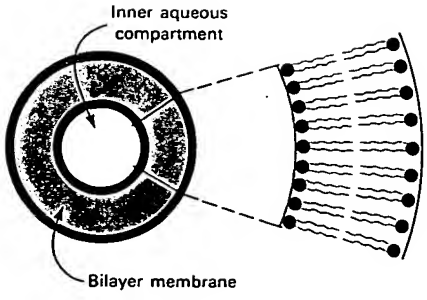

Figure 12-12
Diagram of a lipid vesicle.